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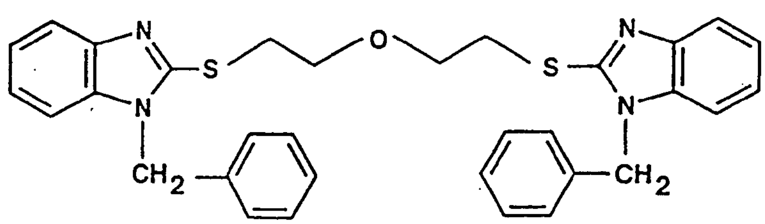
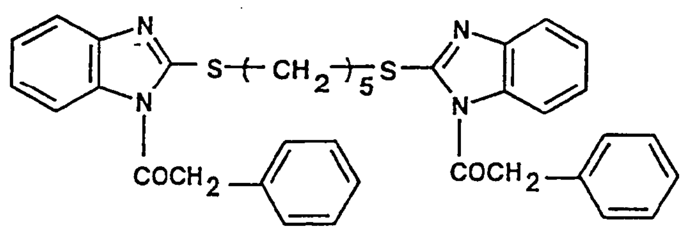
(54) **2-MERCAPTOBENZIMIDAZOLE DERIVATIVE AND ANTIHYPERLIPEMIC OR ANTIARTERIOSCLEROTIC AGENT CONTAINING THE SAME**

(57) 2-Mercaptobenzimidazole derivatives represented by the following formulae, analogs and salts thereof are disclosed:





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Descripti n

Technical Field

The present invention relates to 2-mercaptobenzimidazoles, in particular, bis-type 2-mercaptobenzimidazole compounds. The 2-mercaptobenzimidazole compounds are usable as medicines such as antihyperlipemic and antiarteriosclerotic agents and additives for silver halide photosensitive materials, for liquid crystals and the like.

In particular, the 2-mercaptobenzimidazole derivatives of the present invention are capable of preventing macrophages from foaming which causes arteriosclerosis.

Background of the Invention

As the standard of living is being raised, foods having a high colory and high cholesterol content are increasing in our eating habits. Furthermore, aging society is now being advanced to accelerate the increase in the number of patients suffering from hyperlipemia and arteriosclerosis caused by hyperlipemia. This is a serious social problem.

In the pharmacotherapy for hyperlipemia and arteriosclerosis, the reduction in the lipid concentration in the blood is mainly conducted, but no medicine capable of reducing the arteriosclerotic nidi per se has been developed yet.

Since patients suffering from arteriosclerosis have characteristic lesions, i.e. thickening of intima and cumulation of lipids, medicines effective in reducing the lipid concentration in the blood are used in the pharmacotherapy as described above. However, on the basis of the recent biochemical knowledge, it has been found that foaming of macrophages is a main cause for the formation of the arteriosclerotic lesions. It is, therefore, expected that the arteriosclerotic lesions per se can be reduced by inhibiting the foaming of macrophages.

Disclosure of the Invention

The object of the present invention is to provide new compounds effective for the treatment of patients suffering from hyperlipemia and arteriosclerosis.

Another object of the present invention is to provide an antihyperlipemic agent or an antiarteriosclerotic agent.

The above-described objects and other objects of the present invention will be apparent from the following description and Examples.

After investigations made for the purpose of attaining the above-described objects, the inventors have found that a specified benzimidazole compound has an ACAT inhibition effect, effect of inhibiting the transportation of cholesterol in the cells, excellent effect of decreasing the blood cholesterol and effect of inhibiting the foaming of macrophages. The present invention has been completed on the basis of this finding.

In the first embodiment of the present invention, there are provided 2-mercaptobenzimidazole derivatives represented by the following formulae I to III or salts thereof:

The Best Mode for Carrying Out the Invention

The detailed description will be made on the compounds of the present invention.

In the formula I, the alkyl groups represented by R_1 and R_2 include those having 1 to 18 carbon atoms (such as methyl, ethyl, butyl, octyl, dodecyl and octadecyl groups), preferably those having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups). Particularly preferred alkyl groups are those having 1 to 3 carbon atoms (such as methyl, ethyl, propyl and trifluoro groups). The alkyl groups may be linear, branched or cyclic alkyl groups which may have a substituent. The halogen atoms include fluorine, chlorine, bromine and iodine atoms. Among them, fluorine, chlorine and bromine atoms are preferred. Chlorine atom is particularly preferred. When L_1 is a pentamethylene group, both R_1 and R_2 may be hydrogen atoms.

In the formula II, the halogen atoms represented by R_3 and R_4 include fluorine, chlorine, bromine and iodine atoms. Among them, fluorine, chlorine and bromine atoms are preferred. Chlorine atom is particularly preferred. The alkyl groups include those having 1 to 18 carbon atoms (such as methyl, butyl, octyl, dodecyl and octadecyl groups), preferably those having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups). Particularly preferred alkyl groups are those having 1 to 3 carbon atoms (such as methyl, ethyl, propyl and trifluoro groups). The alkoxy groups include those having 1 to 18 carbon atoms (such as methoxy, butoxy, octyloxy, dodecyloxy and octadecyloxy groups), preferably those having 1 to 8 carbon atoms (such as methoxy, ethoxy, butoxy and octyloxy groups). Particularly preferred alkoxy groups are those having 1 to 3 carbon atoms. The alkoxycarbonyl groups include those having 1 to 18 carbon atoms (such as methoxycarbonyl, butoxycarbonyl, octyloxycarbonyl, d odecyloxycarbonyl and octadecyloxycarbonyl groups), preferably those having 1 to 8 carbon atoms (such as methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl and octyloxycarbonyl groups). Particularly preferred alkoxycarbonyl groups are those having 1 to 3 carbon atoms. The carbamoyl groups include those having 0 to 18 carbon atoms (such as carbamoyl, methylcarbamoyl, diethylcarbamoyl, octylcarbamoyl, hexadecylcarbamoyl and phenylcarbamoyl groups), preferably those having 0 to 8 carbon atoms (such as methylcarbamoyl, diethylcarbamoyl and octylcarbamoyl groups).

The sulfamoyl groups include those having 0 to 18 carbon atoms (such as sulfamoyl, methylsulfamoyl, diethylsulfamoyl, octylsulfamoyl, hexadecylsulfamoyl and phenylsulfamoyl groups), preferably those having 0 to 8 carbon atoms (such as sulfamoyl, methylsulfamoyl, diethylsulfamoyl and octylsulfamoyl groups). The acylamino groups include those having 1 to 18 carbon atoms (such as acetylamino, butanoylamino, octanoylamino, hexadecanoylamino and benzoylamino groups), preferably those having 1 to 8 carbon atoms (such as acetylamino, butanoylamino and octanoylamino groups). The sulfonylamino groups include those having 1 to 18 carbon atoms (such as methanesulfonylamino, butanesulfonylamino, octanesulfonylamino, hexadecanesulfonylamiono and benzenesulfonylamino groups), preferably those having 1 to 8 carbon atoms (such as methanesulfonylamino, butanesulfonylamino, octanesulfonylamino and benzenesulfonylamino groups). These alkyl groups may be linear, branched or cyclic and the alkyl and aryl groups may further have a substituent.

Among them, the halogen atoms, alkyl groups, alkoxy groups, alkoxycarbonyl groups, sulfamoyl groups and nitro group are preferred.

In the formula II, the alkyl groups represented by R_5 and R_6 include those having 1 to 18 carbon atoms (such as methyl, ethyl, butyl, octyl, dodecyl and octadecyl groups), preferably those having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups), which may be either linear or branched. The acyl groups include alkanoyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, sulfamoyl and carbamoyl groups. The alkanoyl groups include those having 1 to 18 carbon atoms (such as acetyl, butanoyl, octanoyl and octadecanoyl groups), preferably those having 1 to 8 carbon atoms (such as acetyl, butanoyl and octanoyl groups). The alkanoyl groups may be linear, branched or cyclic, and the alkyl or aryl group may further have a substituent. The arylcarbonyl groups include those having 6 to 18 carbon atoms (such as benzoyl and naphthoyl groups) which may further have a substituent. The alkoxycarbonyl groups include those having 1 to 18 carbon atoms (such as methoxycarbonyl, ethoxycarbonyl, octyloxycarbonyl and octadecylcarbonyl groups), preferably those having 1 to 8 carbon atoms (such as methoxycarbonyl, ethoxycarbonyl and octyloxycarbonyl grups). The alkoxycarbonyl groups may be linear, branched or cyclic, and they may further have a substituent.

The alkylsulfonyl groups and arylsulfonyl groups include those having 1 to 18 carbon atoms and those having 6 to 18 carbon atoms, respectively, (such as methanesulfonyl, butanesulfonyl, hexadecanesulfonyl, benzenesulfonyl and naphthalenesulfonyl groups) which may further have a substituent. The alkoxycarbonyl groups include those having 1 to 18 carbon atoms (such as methoxycarbonyl, ethoxycarbonyl, octyloxycarbonyl and tetradecyloxycarbonyl groups), preferably those having 1 to 8 carbon atoms (such as methoxycarbonyl, ethoxycarbonyl and octyloxycarbonyl groups) which may further have a substituent. The sulfamoyl groups include those having 0 to 18 carbon atoms (such as sulfamoyl, methylsulfamoyl, diethylsulfamoyl, octylsulfamoyl, hexadecylsulfamoyl and phenylsulfamoyl groups), preferably those having 0 to 8 carbon atoms (such as sulfamoyl, methylsulfamouyl, diethylsulfamoyl and octylsulfamoyl groups) which may further have a substituent. The carbamoyl groups include those having 0 to 18 carbon atoms (such as carbamoyl, methylcarbamoyl, diethylcarbamoyl, octylcarbamoyl, hexad cylcarbamoyl and phenylcarbamoyl groups), preferably those having 0 to 8 carbon atoms (such as methylcarbamoyl, diethylcarbamoyl and octylcarbamoyl groups) which may further have a substituent.

Among the compounds of the formula II-I, those of the following groups (i) to (iii) are particularly preferred from the viewpoint of the pharmacological effect:

(i) Compounds in which one of R_{31} and R_{32} and one of R_{41} and R_{42} are hydrogen and the other is a lower alkyl, halogen (particularly chlorine), nitro or lower acylamino, and each of R_5 and R_6 is a lower alkyl or lower alkanoyl.
(ii) Compounds in which all of R_{31}, R_{32}, R_{41} and R_{42} are hydrogen, and each of R_5 and R_6 is a lower alkanoyl or lower alkyl. L_2 is desirably an alkylene group having 4 to 10 carbon atoms, preferably 4 to 8 carbon atoms. Namely, L_2 is preferably an alkylene-phenylene-alkylene group (the alkylene having desirably 1 to 2 carbon atoms).
(iii) Compounds in which each of R_{31}, R_{32}, R_{41} and R_{42} is a halogen (particularly chlorine) or lower alkyl, and each of R_5 and R_6 is a lower alkanoyl or lower alkyl group.

L_2 in the above-described compounds (i) and (iii) is desirably an alkylene group having 4 to 10 carbon atoms, preferably 4 to 8 carbon atoms. In the compounds (i) to (iii), the term "lower" indicates that it has 1 to 3 carbon atoms.

The compounds represented by the formulae I-I, I-a and II-I may be in the form of a salt thereof. The salts which can be formed include, for example, hydrochlorides, bromates, nitrates, sulfates, phosphates, toluenesulfonates and the like.

The alkyl and acyl groups represented by R_5 and R_6 in the formulae II and II-I are particularly preferably those free from aryl groups.

In the formulae I, II, I-I, I-a and II-I, particularly preferred L_1 and L_2 are alkylene groups havingt 4 to 8 carbon atoms.

The description will be made on the formula III.

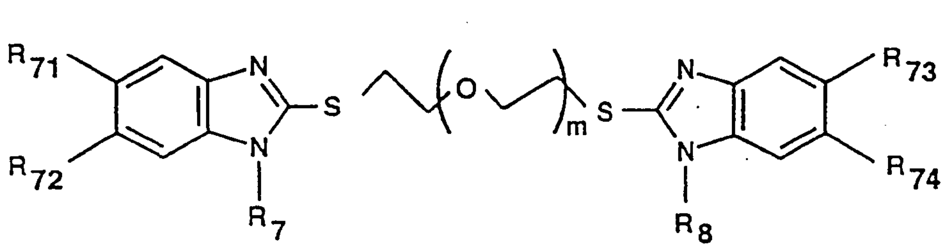
The alkyl groups represented by R_7 and R_8 in the formula III are those having 1 to 18 carbon atoms (such as methyl, ethyl, butyl, octyl, dodecyl and octadecyl groups), preferably those having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups) . The alkylcarbonyl groups are those having 1 to 18 carbon atoms (such as acetyl, butanoyl, octanoyl, tetradecanoyl and octadecanoyl groups), preferably those having 1 to 8 carbon atoms (such as acetyl, butanoyl and octanoyl groups). The alkyl groups contained in these groups may be linear, branched or cyclic, and they may further have a substituent. The most preferred alkyl groups are linear alkyl groups. The alkyl groups having a substituent are preferably those having an aryl group, particularly phenylalkylene groups in which the alkylene group has 1 to 3 carbon atoms.

The halogen atoms represented by R_9 and R_{10} in the formula III include fluorine, chlorine, bromine and iodine atoms. Among them, fluorine, chlorine and bromine atoms are preferred. Chlorine atom is particularly preferred. The alkyl groups are those having 1 to 18 carbon atoms (such as methyl, butyl, octyl, dodecyl and octadecyl groups), preferably those having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups).

The compounds represented by the formula III may be in the form of a salt thereof. The salts which can be formed include, for example, hydrochlorides, bromates, nitrates, sulfates, phosphates, toluenesulfonates and the like.

The particularly preferred compounds of the formula III are those of the following formula III-a:

III − a



wherein R_7 and R_8 are as defined above, R_{71} and R_{72} are the same as R_9, and R_{73} and R_{74} are the same as R_{10}.

In the formula III-a, R_7 and R_8 are preferably the same as each other.

In the formula III-a, if is preferred that the combination of R_{71} and R_{72} is the same as the combination of R_{73} and R_{74} (namely, $R_{71} = R_{73}$ and $R_{72} = R_{74}$ or $R_{71} = R_{74}$ and $R_{72} = R_{73}$).

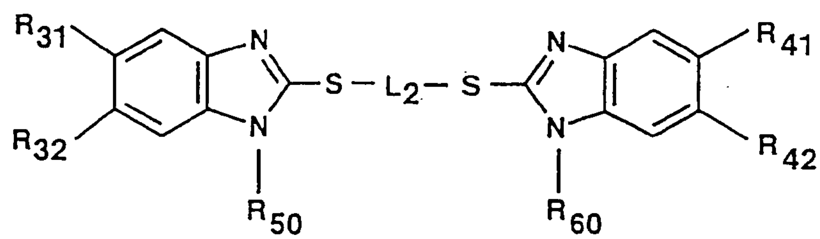
The compounds represented by the formulae III-a may be in the form of a salt thereof. The salts which can be formed include, for example, hydrochlorides, bromates, nitrates, sulfates, phosphat s and toluenesulfonates.

The alkyl and alkylcarbonyl groups represented by R_7 and R_8 in the formula III-a are particularly preferably those free from aryl groups as a substituent. Linear alkyl groups and linear alkylcarbonyl groups are more preferred.

Among the compounds of the formula III-a, those of the following groups (i) to (iv) are particularly preferred:

The particularly preferred compounds of the formula IV are those of the following formula IV-a:

IV − a



wherein L_2, R_{50} and R_{60} are as defined above, R_{31} and R_{32} are the same as R_3, and R_{41} and R_{42} are the same as R_4.

The preferred substituents in the formula IV are also prefered in the formula IV-a.

In the formula IV-a, R_{50} and R_{60} are preferably the same as each other.

In the formula IV-a, it is further preferred that the combination of R_{31} and R_{32} is the same as the combination of R_{41} and R_{42} (namely, R_{31}=R_{41} and R_{32}=R_{42} or R_{31}=R_{42} and R_{32}=R_{41}).

The compounds represented by the formula IV-a may form a salt. The salts which can be formed by these compounds include, for example, hydrochlorides, bromates, nitrates, sulfates, phosphates, toluenesulfonates and the like.

Among the compounds of the formula IV-a, those of the following groups (i) to (v) are particularly preferred from the viewpoint of the pharmacological effect:

(i) Compounds in which all of R_{31} , R_{32}, R_{41} , R_{42}, R_{50} and R_{60} each represent a hydrogen, and L_2 represents an alkylene group having 4 to 10 carbon atoms, preferably 4 to 8 carbon atoms, namely, L_2 is preferably an alkylene-phenylene-alkylene group (the alkylene having desirably 1 to 2 carbon atoms).

(ii) Compounds in which one of R_{31} and R_{32} and one of R_{41} and R_{42} are a hydrogen, and the other is a lower alkyl, halogen (particularly chlorine), nitro or lower acylamino and R_{50} and R_{60} each represent a hydrogen, lower alkyl or lower alkanoyl.

(iii) Compounds in which R_{31}, R_{32}, R_{41} and R_{42} each represent a halogen (particularly chlorine), and R_{50} and R_{60} each represent a hydrogen.

(iv) Compounds in which R_{31}, R_{32}, R_{41} and R_{42} each represent a hydrogen, and R_{50} and R_{60} each represent a lower alkanoyl or lower alkyl, and L_2 is the same as that in (i).

(v) Compounds in which R_{31}, R_{32}, R_{41} and R_{42} each represent a halogen (particularly chlorine) or lower alkyl, and R_{50} and R_{60} each represent a lower alkanoyl or lower alkyl.

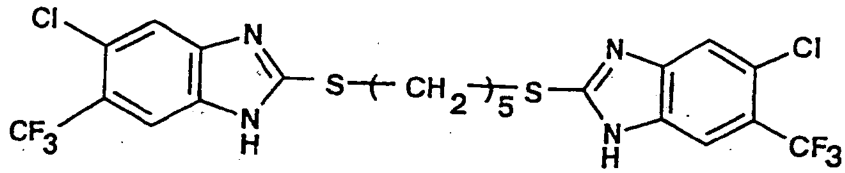
L_2 in the above-described compounds (ii), (iii) and (v) is desirably an alkylene group having 4 to 10 carbon atoms, preferably 4 to 8 carbon atoms. In the compounds (i) to (v), the term "lower" indicates that it has 1 to 3 carbon atoms.

The alkyl and acyl groups represented by R_{50} and R_{60} in the formulae IV and IV-a are particularly preferably those free from aryl groups. They are more preferably a linear alkyl group or linear alkylacyl group.

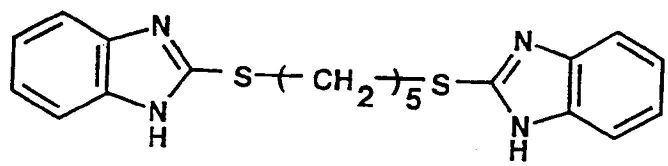
In the formulae IV and IV-a, particularly preferred L_2 is an alkylene group having 4 to 8 carbon atoms.

Examples of typical benzimidazole derivatives of the formulae I to III in the present invention are given below. The numerals (1) to (22) for the compounds of the formula (III) are the same as the numerals for the synthesis examples in Example 2.

(I - 6)



(I - 7)



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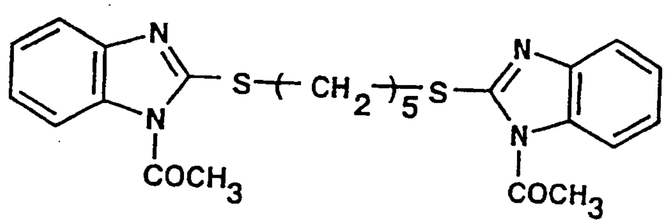

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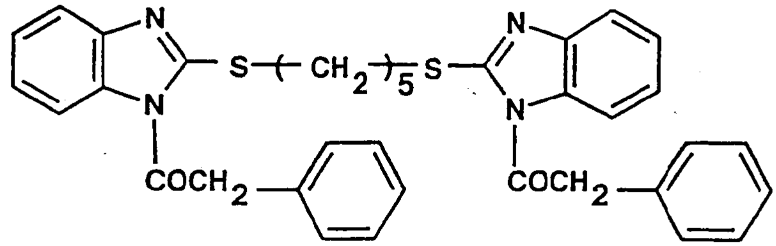

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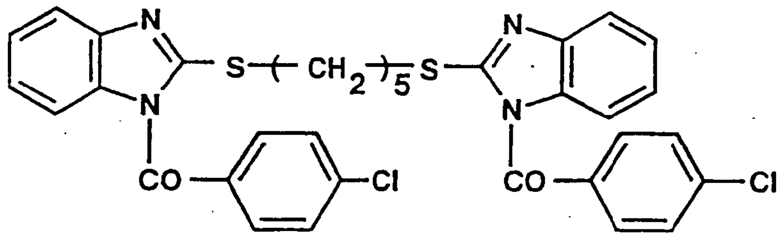

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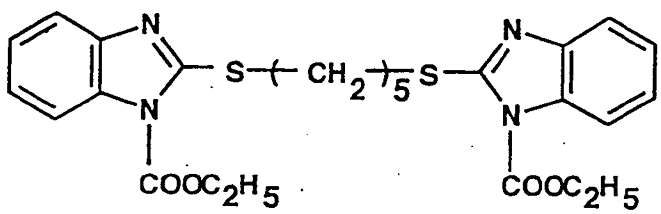

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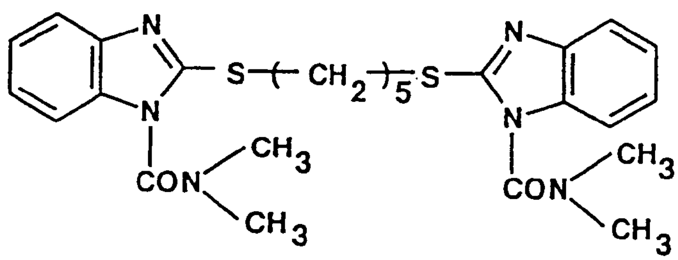

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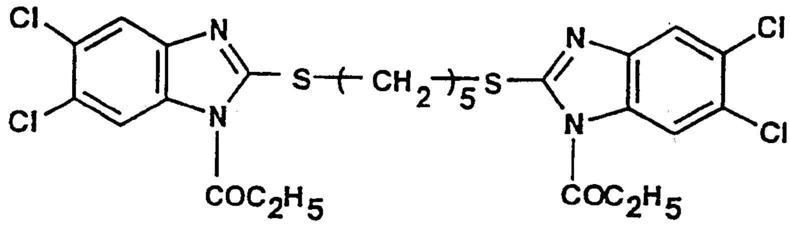

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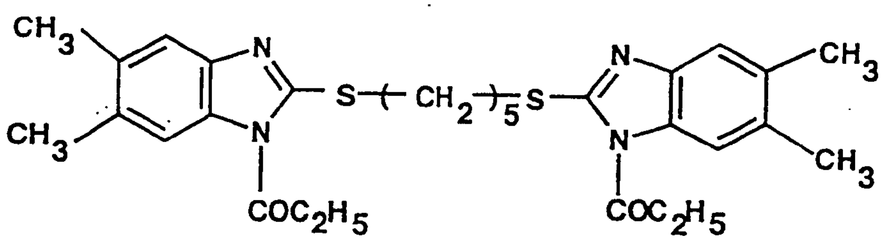

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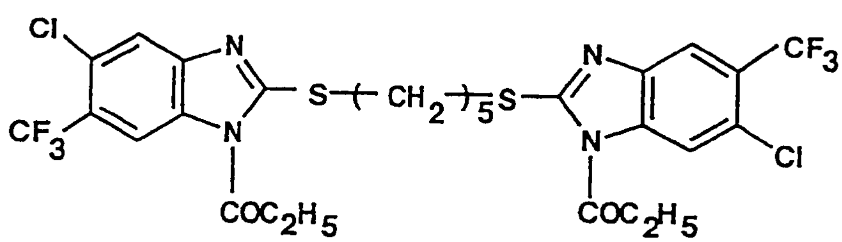

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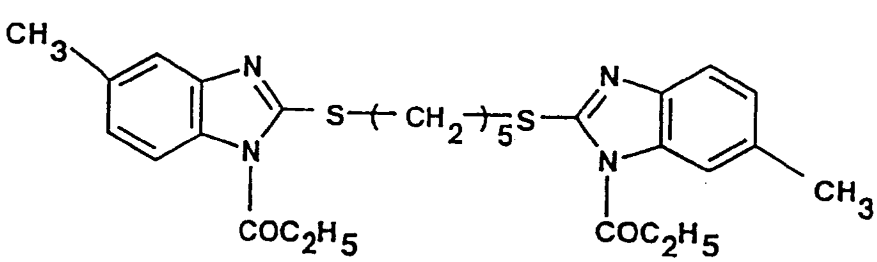

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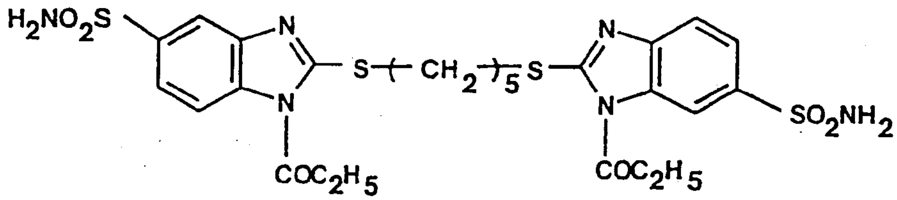

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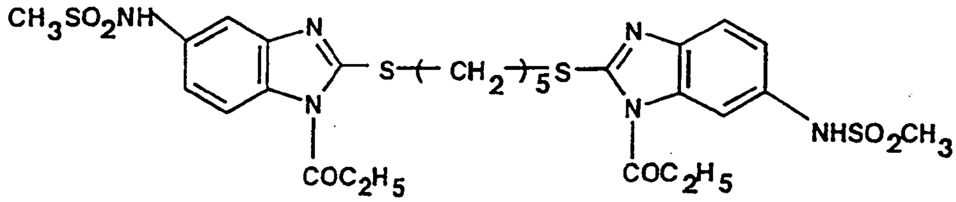

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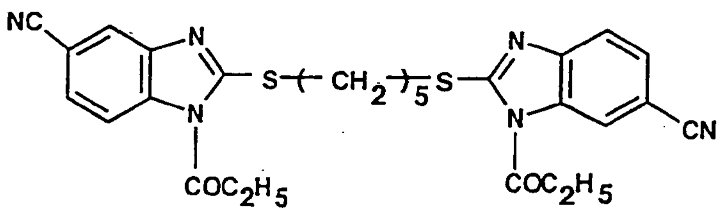

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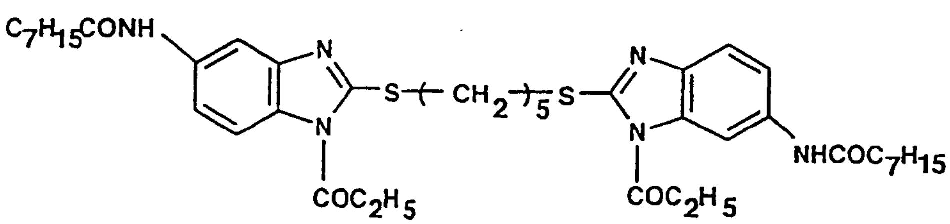

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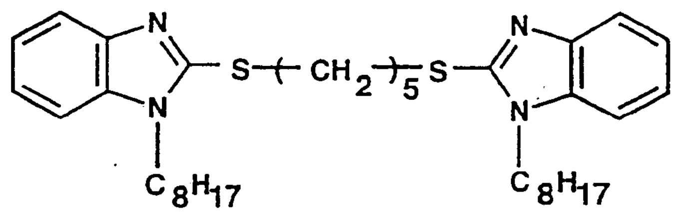

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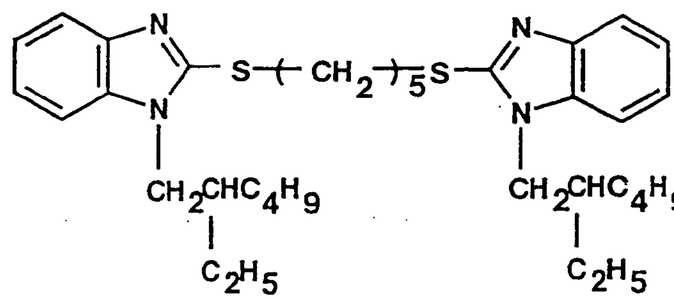

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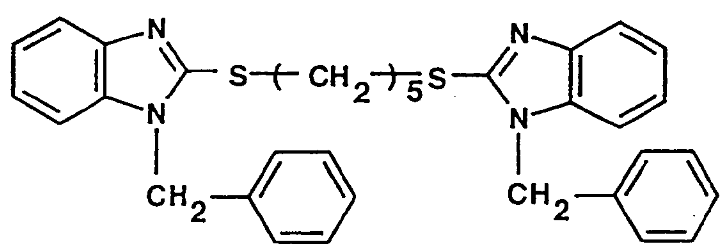

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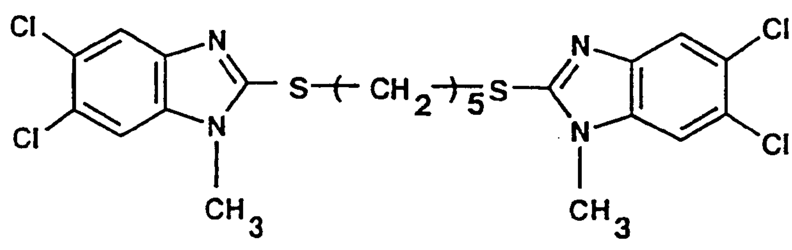

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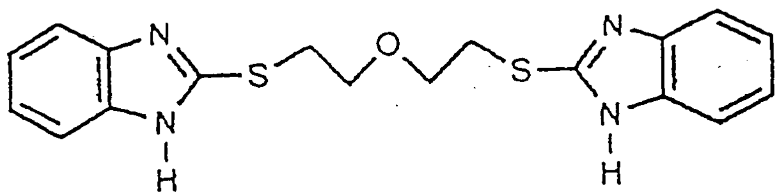

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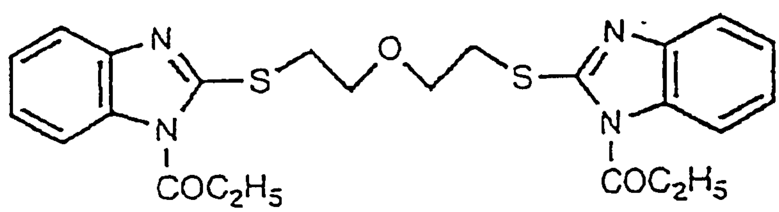

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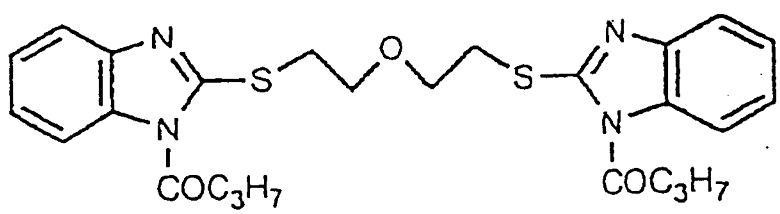

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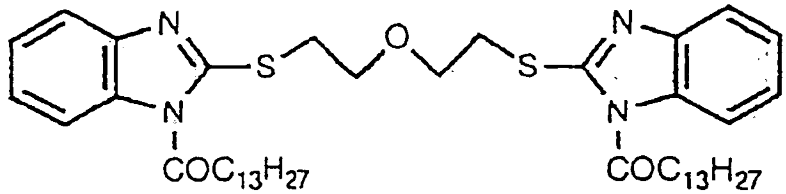
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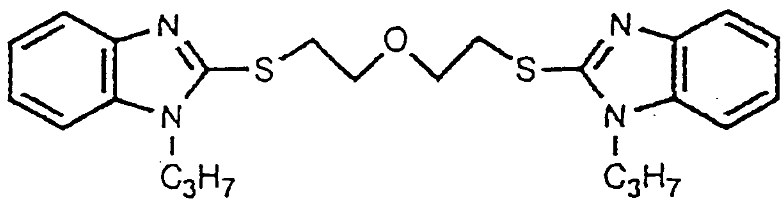
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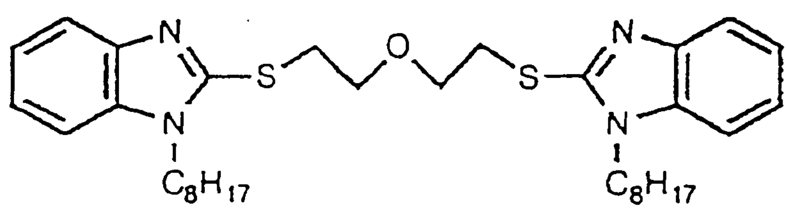
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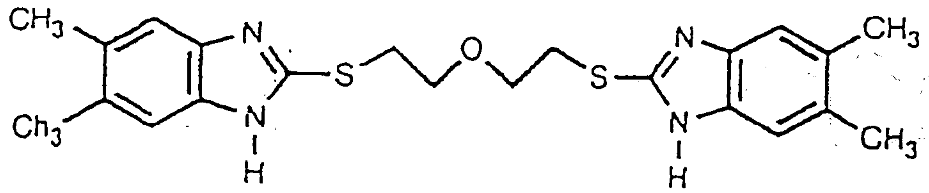

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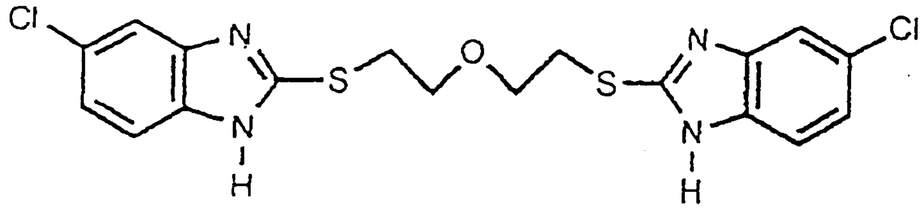

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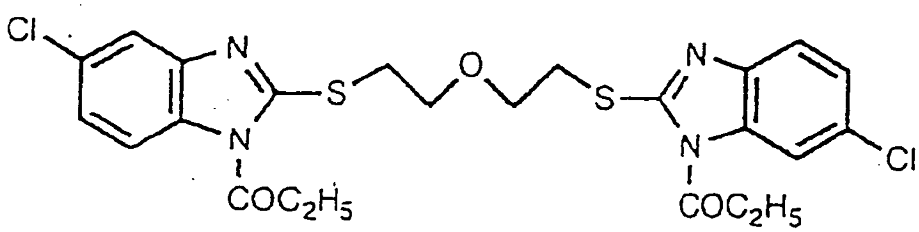

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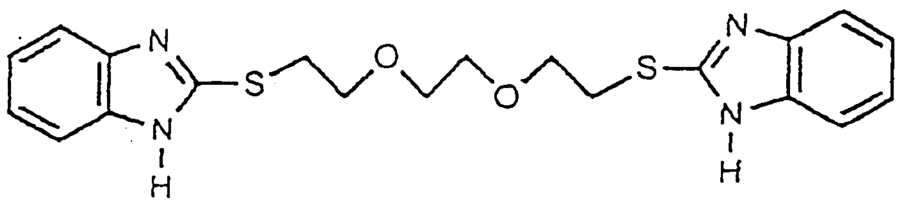

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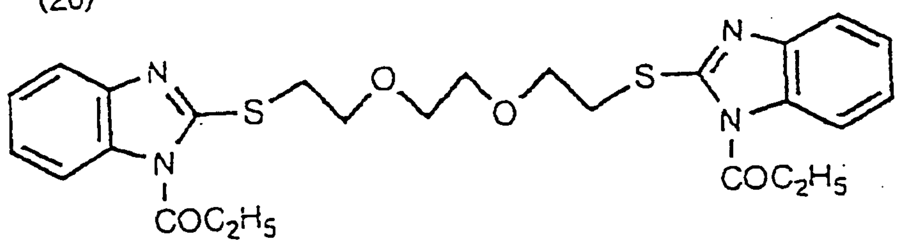

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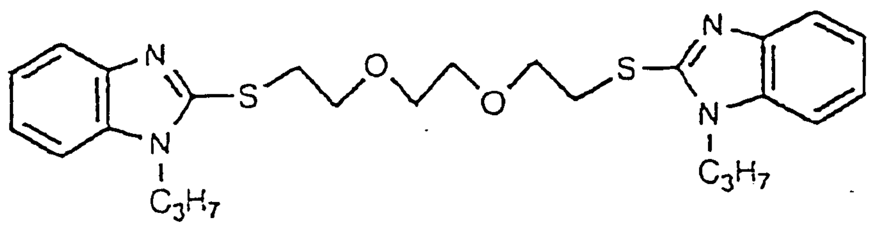

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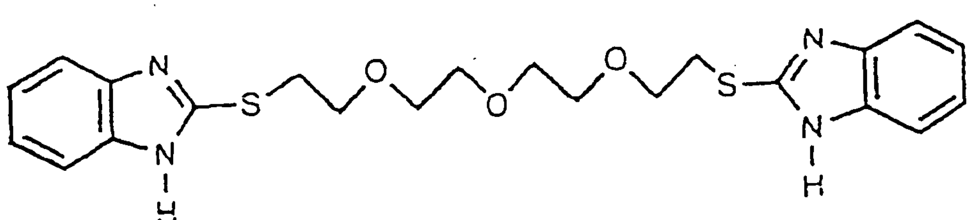

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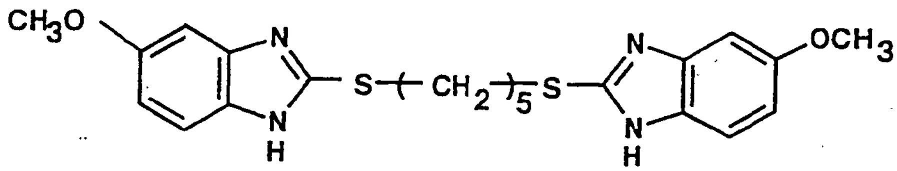

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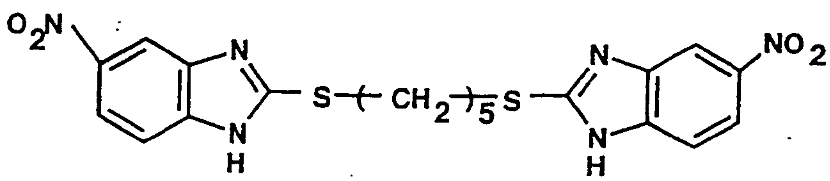

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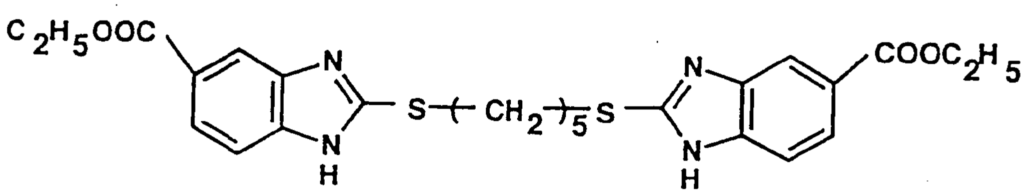

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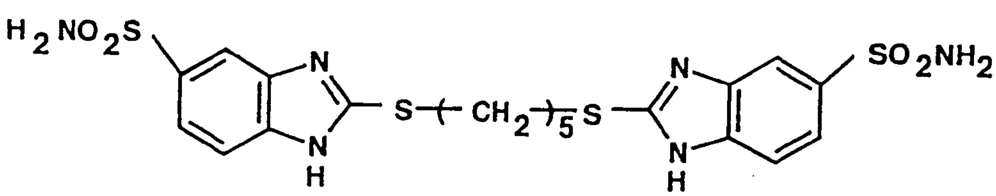

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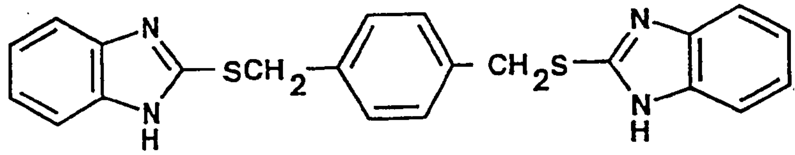

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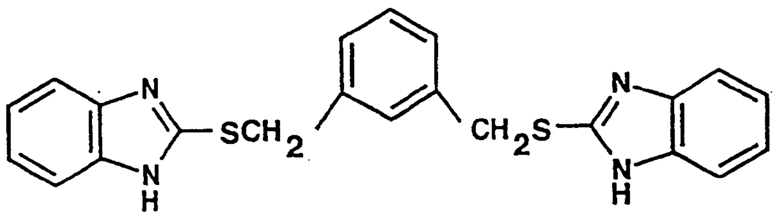
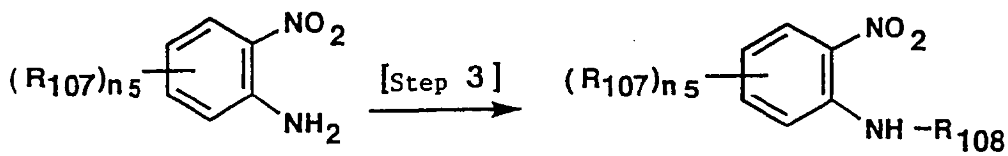


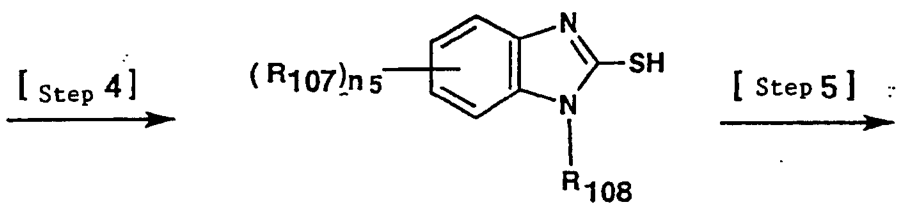
The compounds represented by the formula (IV) include compounds (I-1) to (I-7) and (II-1) to (II-36) in addition to those given above.

2-Mercaptobenzimidazole derivatives represented by the formula I, I-I, I-a, II, II-a or VI can be produced by the following reaction scheme I (formulae 1, 2 and 3):

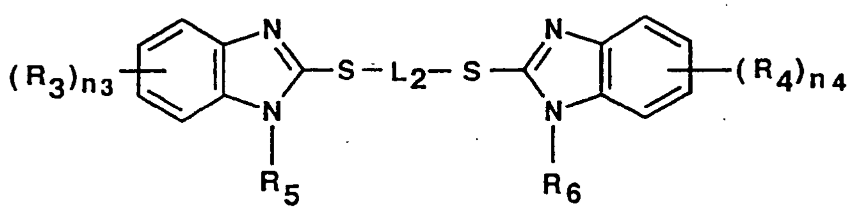
(formula-3)



(VII) (VIII)



(IX)



(II -②)

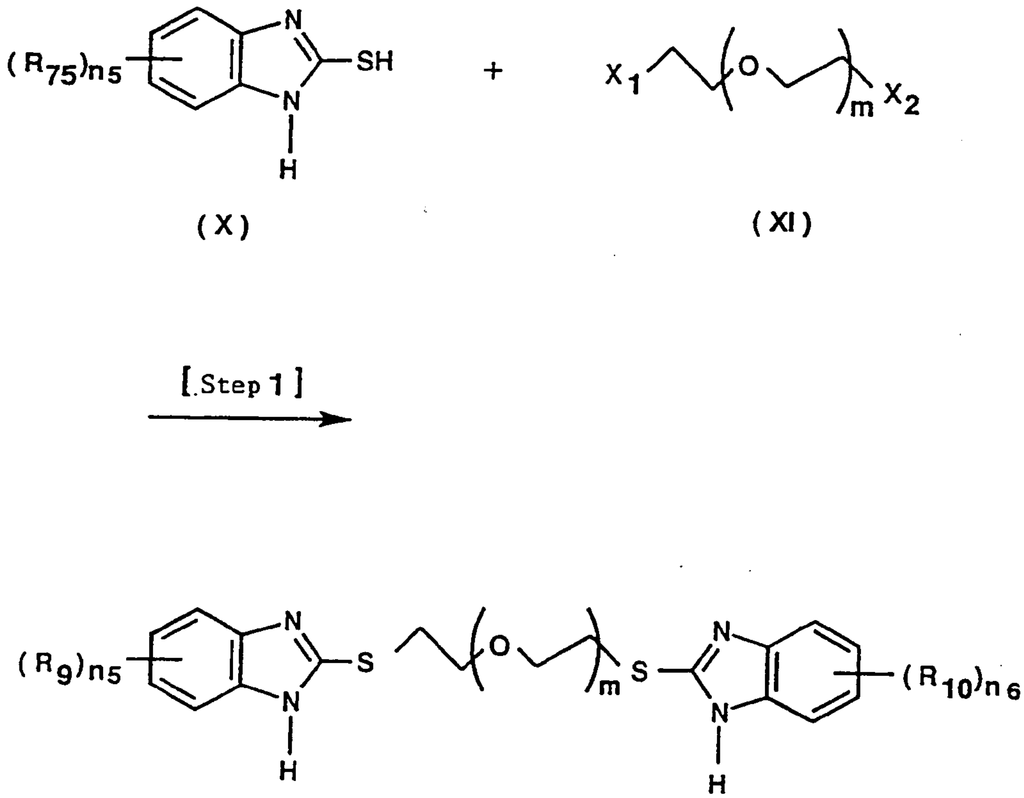
wherein R_1, R_2, R_3, R_4, R_5, R_6, n_1, n_2, n_3, n_4, L_1 and L_2 are as defined above, R_{107} is the same as R_1, R_2, R_3 and R_4, R_{108} is the same as R_5 and R_6, n_5 is the same as n_1, n_2, n_3 and n_4, and X_1 and X_2 each represent a halogen atom or a group which is split off by the nucleophilic substitution reaction such as a sulfonic ester.

(Formula-1)

[Step 1] Although 2-Mercaptobenzimidazoles (V) used for this reaction are available on the market or known compounds, these compounds can be usually synthesized by a method described in Org. Syn., Col. Vol. 4, p. 569. Compounds (1- ①) can be synthesized by reacting a corresponding 2-mercaptobenzimidazole (V) with a bonding group (VI) having two splitting-off groups. Although it is usually desirable to conduct this reation in the presence of a basic catalyst such as sodium hydroxide, potassium carbonate, triethylamine or sodium ethylate as a deacidifying agent in an ordinary organic solvent [such as ethanol, acetonitrile, acetone, ethyl acetate, DMF (dimethylformamide) or THF (tetrahydrofuran)], this reaction can be also conducted under heating in the absence of any catalyst in an alcohol.

When the basic compound is used, the reaction temperature which varies depending on the substrate and solvent is usually 0 to 150 °C, preferably 20 to 100°C . On the other hand, when the reaction is conducted in the absence of the catalyst in an alcohol, the reaction temperature is preferably 50 to 120 °C.

(formula-4)



(III -①)

The compound (XI) is used in an amount of 0.35 to 0.7 mol, preferably 0.45 to 0.55 mol, per mol of the compound (X), and an insufficient or excess amount thereof is undesirable for inhibiting side reactions in this step.

(Formula-5)

[Step 2] Where the compound (III-①) can be acylated to form a compound (III-②), it can be carrid out by reacting compound (III-①) with a corresponding acid halide in the presence of a basic catalyst (such as potassium carbonate, triethylamine or pyridine) as the deacidifying agent in an ordinary inert solvent [such as acetonitrile, ethyl acetate, THF, DMF or DMAc (dimethylacetamide)]. However, when DMF, DMAc, acetonitrile or the like having a high polarity is used, the basic catalyst is unnecessary.

The amount of the solvent used in this step is preferably 2 to 50 parts per part of the compound (III-①), and that of the acid halide is 1.8 to 2.4 mol per mol of the compound (III-①). Although the reaction can proceed at 30 to 150°C, it is preferably conducted at 50 to 100 °C.

When n_5 and n_6 are 1, an asymmetrically substituted product is preferentially obtained as shown in most synthesis examples in Example 2.

In the alkylation of the compound (III- ①) to form the compound (III-②), the former is reacted with an alkyl halide or alkyl tosylate in the presence of a basic catalyst such as sodium hydroxide, potassium carbonate, triethylamine or sodium ethylate as the deacidifying agent in an ordinary organic solvent [such as ethanol, acetonitrile, acetone, ethyl acetate, DMF (dimethylformamide) or THF (tetrahydrofuran)]. The reaction temperature which varies depending on the substrate and solvent is usually 0 to 100 °C, preferably 20 to 60 °C.

The antihyperlipemic agent or antiarteriosclerotic agent of the present invention may contain one or more compounds represented by the formula III or IV. Such an agent may be used in combination with a known compatible antihyperlipemic agent or antiarteriosclerotic agent used hitherto in this technical field. The antihyperlipemic agent or antiarteriosclerotic agent used hitherto include Melinamide, Probucol, Mevalotin, etc.

The medicine of the present invention is administered orally, by injection (mainly intramuscular, intravenous or subcutaneous injection) or the like, and it is prepared in a dosage form suitable for the medication. The medicine is usable in the form of an intravenous preparation such as tablets, powder, granules, capsules, syrup, emulsion, suspension or solution, or of an injection. A carrier or diluent suitable for the dosage form and also a suitable physiologically active substance are usable for the preparation.

Examples of preferred medical carriers and diluents for the medicines usable in combination with the compound of the formula III or IV include glucose; saccharose; lactose; ethyl alcohol; glycerol; mannitol; sorbitol; pentaerythritol; diethylene glycol, triethylene glycol, ethylene glycol, propylene glycol, dipropylene glycol, polyethylene glycol 400 and other polyethylene glycols; mono-, di- and triglycerides of saturated fatty acids such as glyceryl trilaurate, glyceryl monostearate, glyceryl tristearate and glyceryl distearate; pectin; starch; corn starch; alginic acid; xylose; talc, lycopodium spores; oils and fats such as olive oil, peanut oil, castor oil, corn oil, wheat malt oil, sesame oil, cotton seed oil, sunflower oil and cod liver oil; gelatin, lecithin; silica; cellulose; cellulose derivtives such as methylhydroxypropylcellulose, methylcellulose, hydroxyethylcellulose and carboxymethylcellulose calcium; magnesium salts or calcium salts of fatty acids having 12 to 22 carbon atoms such as calcium stearate, calcium laurate, magnesium oleate, calcium palmitate, calcium behenate and magnesium stearate; cyclodextrins such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxyethyl-β -cyclodextrin, hydroxypropyl-β-cyclodextrin, dihydroxypropyl-β-cyclodextrin, carboxymethyl-β-cyclodextrin and dimethyl-β-cyclodextrin; emulsifying agents such as esters of a saturated or unsaturated fatty acid having 2 to 22, particularly 10 to 18 carbon atoms, with a monohydric aliphatic alcohol (for example, an alkanol having 1 to 20 carbon atoms) or polyhydric alcohol such as glycol, glycerol, diethylene glycol, pentaerythritol, ethyl alcohol, butyl alcohol or octadecyl alcohol; silicones such as dimethylpolysiloxanes; and pyrogen-free distilled water.

The dosage of the medicine of the present invention, which varies depending on the disease, age, body weight and symptoms of the patient and route of administration, is usually in the range of 0.1 to 500 mg, preferably 0.2 to 100 mg, (in terms of the active ingredient) per kg-body weight / day for adults.

The present invention provides the medicine having excellent effect of decreasing blood cholesterol and inhibiting the foaming of macrophases and only a low toxicity and capable of being administered for a long period of time for exhibiting excellent therapeutic effect against hypeylipemia and arteriosclerosis.

The following Examples will further illustrate the present invention.

Example 1

The description will be made on examples of synthesis of the compounds according to the present invention.

Elementary analysis for $C_{18}H_{18}N_4S_2$:			
Calculated:	C 60.98;	H 5.12;	N 15.81 (%)
Found:	C 60.77;	H 5.36;	N 15.70 (%)

(5) Synthesis of 1,5-bis(5-methyl-2-benzimidazoylthio)pentane (compound I-1):

8.1 g (yield: 82 %) of the intended compound was obtained from 8. 2 g of 2-mercapto-5-methylbenzimidazole and 5.5 g of 1,5-dibromopentane in the same manner as in (1).

Melting point: 161 to 163°C

Elementary analysis for $C_{21}H_{24}N_4S_2$:			
Calculated:	C 63.60;	H 6.10;	N 14.13 (%)
Found:	C 63.42;	H 6.02;	N 14.29 (%)

(6) Synthesis of 1,5-bis(5-methoxyl-2-benzimidazoylthio)pentane (compound IV-4):

3.8 g (yield: 88 %) of the intended compound was obtained from 3. 6 g of 2-mercapto-5-methoxybenzimidazole and 2.2 g of 1,5-dibromopentane in the same manner as in (1).

Melting point: 170 to 172°C

Elementary analysis for $C_{21}H_{24}N_4O_2S_2$:			
Calculated:	C 58.85;	H 5.64;	N 13.08 (%)
Found:	C 58.69;	H 5.49;	N 13.12 (%)

(7) Synthesis of 1,5-bis(5-chloro-2-benzimidazoylthio)pentane (compound I-3):

12 g of 5-chloro-2-mercaptobenzimidazole and 7.45 g of 1,5-dibromopentane were dissolved in 200 ml of ethanol, and the thus-obtained solution was refluxed under stirring on a water bath for 12 hours. After cooling, it was neutralized with 35 ml of 2 N aqueous sodium hydroxide solution. 200 ml of water was added to the oily substance thus formed. The aqueous layer was removed by decantation. The oily substance was dispersed in 500 ml of acetonitrile. 60 ml of hydrochloric acid was added to the dispersion, and the resultant mixture was stirred for 2 hours. Crystals thus formed were collected by filtration, and then washed with acetonitrile. After drying, 32 g of the intended compound was obtained in the form of its dihydrochloride (yield: 91 %).

Melting point: 182 to 188°C

Elementary analysis for $C_{19}H_{20}N_4S_2Cl_4$:			
Calculated:	C 44.72;	H 3.95;	N 10.98 (%)
Found:	C 44.51;	H 3.73;	N 10.75 (%)

Elementary analysis for $C_{25}H_{30}N_6O_2S_2$:			
Calculated:	C 58.80;	H 5.92;	N 16.46 (%)
Found:	C 58.63;	H 5.86;	N 16.33 (%)

(12) Synthesis of 1,5-bis(5-octanamido-2-benzimidazoylthio)pentane (compound IV-9):

8.3 g of 5-amino-2-mercaptobenzimidazole was suspended in a mixture of 20 ml of dimethylacetamide and 35 ml of acetonitrile. 8.5 g of octanoyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 2 hours, 20 ml of water was added to the reaction mixture. Crystals thus formed were collected by filtration, washed with water and dried to obtain 12.8 g of 2-mercapto-5-octanamidobenzimidazole (yield: 88 %).

5.2 g (yield: 80 %) of the intended compound was obtained from 2. 9 g of 2-mercapto-5-octanamidobenzimidazole and 1.1 g of 1,5-dibromopentane in the same manner as in (1).

Melting point: 132 to 135°C

Elementary analysis for $C_{35}H_{50}N_6O_2S_2$:			
Calculated:	C 64.58;	H 7.74;	N 12.29 (%)
Found:	C 64.42;	H 7.65;	N 12.73 (%)

(13) Synthesis of 1,5-bis(5-methanesulfonamido-2-benzimidazoylthio) pentane (compound IV-10):

2.2 g (yield: 80 %) of the intended compound was obtained from 2. 4 g of 5-methanesulfonamido-2-mercaptobenzimidazole and 1.1 g of 1,5-dibromopentane in the same manner as in (1).

Melting point: 168 to 172°C

Elementary analysis for $C_{21}H_{26}N_6O_4S_4$:			
Calculated:	C 45.47;	H 4.72;	N 15.15 (%)
Found:	C 45.22;	H 4.61;	N 15.28 (%)

(14) Synthesis of 1,5-bis(5-octanesulfonamido-2-benzimidazoylthio) pentane (compound IV-11):

2.2 g (yield: 80 %) of the intended compound was obtained from 3.0 g of 5-octanesulfonamido-2-mercaptobenzimidazole and 1.1 g of 1,5-dibromopentane in the same manner as in (1).

Melting point: 153 to 156°C

Elementary analysis for $C_{35}H_{52}N_6O_4S_4$:			
Calculated:	C 56.12;	H 7.00;	N 11.22 (%)
Found:	C 55.96;	H 6.87;	N 11.12 (%)

Elementary analysis for $C_{22}H_{22}N_4S_2Cl_4$:			
Calculated:	C 48.18;	H 4.04;	N 10.22 (%)
Found:	C 47.97;	H 3.93;	N 10.03 (%)

(20) Synthesis of 1,4-bis(2-benzimidazoylthiomethyl)benzene (compound IV-13):

3.8 g (yield: 95 %) of the intended compound was obtained from 3. 0 g of 2-mercapto-benzimidazole and 1.66 g of p-xylylene dichloride in the same manner as in (1).

Melting point: 267 to 270°C

Elementary analysis for $C_{22}H_{18}N_4S_2$:			
Calculated:	C 65.64;	H 4.51;	N 13.92 (%)
Found:	C 65.45;	H 4.47;	N 13.83 (%)

(21) Synthesis of 1,3-bis(2-benzimidazoylthiomethyl)benzene (compound IV-14):

3.88 g (yield: 97 %) of the intended compound was obtained from 3.0 g of 2-mercapto-benzimidazole and 3.0 g of m-xylylene dibromide in the same manner as in (1).

Melting point: 227 to 229°C

Elementary analysis for $C_{22}H_{18}N_4S_2$:			
Calculated:	C 65.64;	H 4.51;	N 13.92 (%)
Found:	C 65.49;	H 4.42;	N 13.79 (%)

(22) Synthesis of 1,5-bis(1-acetyl-2-benzimidazoylthio)pentane (compound II-1):

0.92 g of 1,5-bis(2-benzimidazoylthio)pentane was suspended in a mixture of 4 ml of dimethylacetamide, 7 ml of acetonitrile and 0.84 ml of triethylamine. 0.4 ml of acetyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 2 hours, 10 ml of acetonitrile and 4 ml of water were added to the reaction mixture. Crystals thus formed were collected by filtration, washed with acetonitrile and dried to obtain 1.0 g of the intended compound (yield: 86 %).

Melting point: 140 to 142°C

Elementary analysis for $C_{23}H_{24}N_4O_2S_2$:			
Calculated:	C 61.10;	H 5.35;	N 12.38 (%)
Found:	C 61.02;	H 5.42;	N 12.16 (%)

Elementary analysis for $C_{35}H_{32}N_4O_2S_2$:			
Calculated:	C 69.51;	H 5.33;	N 9.27 (%)
Found:	C 69.37;	H 5.25;	N 9.34 (%)

(27) Synthesis of 1,5-bis(1-(4-chlorobenzoyl)-2-benzimidazoylthio) pentane (compound II-6):

0.92 g of 1,5-bis(2-benzimidazoylthio)pentane was suspended in a mixture of 4 ml of dimethylacetamide, 7 ml of acetonitrile and 0.84 ml of triethylamine. 0. 70 ml of 4-chlorobenzoyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 2 hours followed by cooling, 10 ml of acetonitrile and 20 ml of water were added to the reaction mixture. The oily product thus formed was collected and then crystallized from acetonitrile + ethanol. The crystals were collected by filtration, washed with acetonitrile and dried to obtain 1.28 g of the intended compound (yield: 79 %).

Melting point: 74 to 76°C

Elementary analysis for $C_{33}H_{26}H_4O_2S_2Cl_2$:			
Calculated:	C 61.39;	H 3.82;	N 8.68 (%)
Found:	C 61.24;	H 3.93;	N 8.53 (%)

(28) Synthesis of 1,5-bis(1-ethoxycarbonyl-2-benzimidazoylthio)pentane (compound II-7):

0.92 g of 1,5-bis(2-benzimidazoylthio)pentane was suspended in a mixture of 4 ml of dimethylacetamide, 7 ml of acetonitrile and 0.84 ml of triethylamine. 0.71 ml of ethyl chlorocarbonate was dropped into the suspension at 50 °C. After stirring at 50 °C for 2 hours followed by cooling, 10 ml of acetonitrile and 4 ml of water were added to the reaction mixture. The crystals thus formed were collected by filtration, washed with acetonitrile and dried to obtain 1.3 g of the intended compound (yield: 100 %).

Melting point: 72 to 74°C

Elementary analysis for $C_{25}H_{28}N_4O_4S_2$:			
Calculated:	C 58.57;	H 5.51;	N 10.93 (%)
Found:	C 58.43;	H 5.62;	N 11.14 (%)

(29) Synthesis of 1,5-bis(1-dimethylcarbamoyl-2-benzimidazoylthio) pentane (compound II-8):

0.92 g of 1,5-bis(2-benzimidazoylthio)pentane was suspended in a mixture of 4 ml of dimethylacetamide, 7 ml of acetonitrile and 0.84 ml of triethylamine. 0.51 ml of dimethylcarbamoyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 3 hours, 20 ml of water was added to the reaction mixture. The oily substance thus formed was extracted with ethyl acetate. After washing with water, the solvent was distilled off under reduced pressure, and the residue was crystallized from hot acetonitrile. The crystals thus formed were collected by filtration, washed with acetonitrile and dried to obtain 0.4 g of the intended compound (yield: 31 %).

Melting point: 245 to 247°C

Elementary analysis for $C_{28}H_{34}N_4O_2S_2$:			
Calculated:	C 64.33;	H 6.56;	N 10.72 (%)
Found:	C 64.21;	H 6.48;	N 10.64 (%)

(33) Synthesis of 1,4-bis(1-propionyl-2-benzimidazoylthiomethyl)benzene (compound II-12):

0.4 g of 1,4-bis(2-benzimidazoylthiomethyl)benzene was suspended in a mixture of 2 ml of dimethylacetamide, 4 ml of acetonitrile and 0.34 ml of triethylamine. 0.2 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 2 hours followed by cooling, 5 ml of acetonitrile and 2 ml of water were added to the reaction mixture. The crystals thus formed were collected by filtration, washed with acetonitrile and dried to obtain 0.42 g of the intended compound (yield: 92 %).

Melting point: 220 to 223°C

Elementary analysis for $C_{28}H_{26}N_4O_2S_2$:			
Calculated:	C 65.34;	H 5.09;	N 10.88 (%)
Found:	C 65.15;	H 4.98;	N 10.62 (%)

(34) Synthesis of 1,3-bis(1-propionyl-2-benzimidazoylthionethyl)benzene (compound II-13):

0.4 g of 1,3-bis(2-benzimidazoylthiomethyl)benzene was suspended in a mixture of 2 ml of dimethylacetamide, 4 ml of acetonitrile and 0.34 ml of triethylamine. 0.2 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 2 hours followed by cooling, 5 ml of acetonitrile and 2 ml of water were added to the reaction mixture. The crystals thus formed were collected by filtration, washed with acetonitrile and dried to obtain 0.45 g of the intended compound (yield: 99 %).

Melting point: 193 to 195°C

Elementary analysis for $C_{28}H_{26}N_4O_2S_2$:			
Calculated:	C 65.34;	H 5.09;	N 10.88 (%)
Found:	C 65.41;	H 5.12;	N 10.73 (%)

(35) Synthesis of 1,5-bis(5,6-dichloro-1-propionyl-2-benzimidazoylthio) pentane (compound II-14):

0.6 g of 1,5-bis(5,6-dichloro-2-benzimidazoylthio)pentane was suspended in a mixture of 2.5 ml of dimethylacetamide, 5 ml of acetonitrile and 0.44 ml of triethylamine. 0.23 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 4 hours followed by cooling, 7 ml of acetonitrile and 3 ml of water were added to the reaction mixture. The crystals thus formed were collected by filtration, washed with acatonitrile and dried to obtain 0.6 g of the intended compound (yield: 95 %).

Melting point: 136 to 138°C

(39) Synthesis of 1-(5-methoxyl-1-propionyl-2-benzimidazoylthio)-5-(6-methoxyl-1-propionyl-2-benzimidazoylthio)pentane (compound II-18):

0.64 g of 1,5-bis(5-methoxyl-2-benzimidazoylthio)pentane was suspended in a mixture of 3.5 ml of dimethylacetamide, 7 ml of acetonitrile and 0.5 ml of triethylamine. 0.29 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 1.5 hours followed by cooling, 10 ml of water was added to the reaction mixture. The oily product thus formed was extracted with ethyl acetate. The extract was washed with water and then the solvent was distilled off under reduced pressure. The residue was crystallized from acetonitrile. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0.52 g of the intended compound (yield: 64 %).

Melting point: 103 to 106°C

Elementary analysis for $C_{27}H_{32}N_4O_4S_2$:			
Calculated:	C 59.97;	H 5.97;	N 10.36 (%)
Found:	C 59.69;	H 5.84;	N 10.23 (%)

(40) Synthesis of 1-(5-propanamido-1-propionyl-2-benzimidazoylthio)-5-(6-propanamido-1-propionyl-2-benzimidazoylthio)pentane (compound II-19):

0.6 g of 1,5-bis(5-propanamido-2-benzimidazoylthio)pentane was suspended in a mixture of 3 ml of dimethylacetamide, 6 ml of acetonitrile and 0.6 ml of triethylamine. 0.33 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 1 hour followed by cooling, 5 ml of acetonitrile and 5 ml of water were added to the reaction mixture. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0.58 g of the intended compound (yield: 89 %).

Melting point: 109 to 112°C

Elementary analysis for $C_{31}H_{38}N_6O_4S_2$:			
Calculated:	C 59.78;	H 6.15;	N 13.50 (%)
Found:	C 59.66;	H 6.09;	N 13.21 (%)

(41) Synthesis of 1-(5-chloro-1-propionyl-2-benzimidazoylthio)-5-(6-chloro-1-propionyl-2-benzimidazoylthio)pentane (compound II-20):

0.51 g of 1,5-bis(5-chloro-2-benzimidazoylthio)pentane dihydrochloride was suspended in a mixture of 3 ml of dimethylacetamide, 6 ml of acetonitrile and 0.65 ml of triethylamine. 0.2 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 1.5 hour followed by cooling, 7 ml of acetonitrile and 3 ml of water were added to the reaction mixture. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0.4 g of the intended compound (yield: 81 %).

Melting point: 95 to 98°C

Elementary analysis for $C_{25}H_{26}N_4O_2S_2Cl_2$:			
Calculated:	C 54.39;	H 4.77;	N 10.20 (%)
Found:	C 54.18;	H 4.62;	N 10.04 (%)

(45) Synthesis of 1-(5-cyano-1-propionyl-2-benzimidazoylthio)-5-(6-cyano-1-propionyl-2-benzimidazoylthio)pentane (compound II-24):

0.42 g of 1,5-bis(5-cyano-2-benzimidazoylthio)pentane was suspended in a mixture of 3 ml of dimethylacetamide, 6 ml of acetonitrile and 0.33 ml of triethylamine. 0.2 ml of propionyl chloride was dropped into the suspension at 50 °C. After stirring at 50 °C for 2 hours followed by cooling, 7 ml of acetonitrile and 3 ml of water were added to the reaction mixture. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0.42 g of the intended compound (yield: 79 %).

Melting point: 128 to 131°C

Elementary analysis for $C_{27}H_{26}N_6O_2S_2$:			
Calculated:	C 61.11;	H 4.94;	N 15.84 (%)
Found:	C 60.97;	H 4.87;	N 15.68 (%)

(46) Synthesis of 1-(5-octanamido-1-propionyl-2-benzimidazoylthio)-5-(6-octanamido-1-propionyl-2-benzimidazoylthio)pentane (compound II-25):

0.65 g of 1,5-bis(5-octanamido-2-benzimidazoylthio)pentane was suspended in a mixture of 3 ml of dimethylacetamide, 6 ml of acetonitrile and 0.6 ml of triethylamine. 0.33 ml of propionyl chloride was dropped into the suspension at 50°C. After stirring at 50 °C for 1 hour followed by cooling, 5 ml of acetonitrile and 5 ml of water were added to the reaction mixture. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0. 65 g of the intended compound (yield: 87 %).

Melting point: 122 to 126°C

Elementary analysis for $C_{41}H_{58}N_6O_4S_2$:			
Calculated:	C 64.53;	H 7.77;	N 11.02 (%)
Found:	C 64.33;	H 7.68;	N 11.08 (%)

(47) Synthesis of 1- (5-octanesulfonamido-1-propionyl-2-benzimidazoylthio)-5-(6-octanesulfonamido-1-propionyl-2-benzimidazoylthio)pentane (compound II-26):

0.75 g of 1,5-bis(5-octanesulfonamido-2-benzimidazoylthio) pentane was suspended in a mixture of 3 ml of dimethylacetamide, 6 ml of acetonitrile and 0.33 ml of triethylamine. 0.2 ml of propionyl chloride was dropped into the suspension at 50 °C. After stirring at 50 °C for 2 hour followed by cooling, 7 ml of acetonitrile and 3 ml of water were added to the reaction mixture. The crystals thus obtained were collected by filtration, washed with acetonitrile and dried to obtain 0.65 g of the intended compound (yield: 76 %).

Melting point: 147 to 150°C

Elementary analysis for $C_{41}H_{62}N_6O_6S_4$:			
Calculated:	C 57.04;	H 7.24;	N 9.74 (%)
Found:	C 57.21;	H 7.08;	N 9.63 (%)

product thus obtained was extracted with ethyl acetate and washed with water twice. The solvent was distilled off under reduced pressure. After the separation and purification by silica gel column chromatography (silica gel 100 g, solvent: chloroform), 0.9 g of the intended compound was obtained as an oily substance (yield: 76 %). (53) Synthesis of 1,5-bis(1-benzyl-2-benzimidazoylthio)pentane (compound II-32):

0.74 g of 1,5-bis(2-benzimidazoylthio)pentane, 0.75 g of benzyl bromide and 0.83 g of potassium carbonate were added to 7 ml of dimethylformamide, and the resultant mixture was stirred at 30°C for 7 hours. After cooling, 10 ml of water was added to the reaction mixture and then the mixture was neutralized with 2 N hydrochloric acid. The oily product thus obtained was extracted with ethyl acetate and washed with water twice. The solvent was distilled off under reduced pressure and the product was crystallized from acetonitrile to obtan 0.82 g of the intended crystals (yield: 75 %).

Melting point: 111 to 113°C

Elementary analysis for $C_{33}H_{32}N_4S_2$:			
Calculated:	C 72.22;	H 5.88;	N 10.21 (%)
Found:	C 71.95;	H 5.76;	N 10.07 (%)

(54) Synthesis of 1,5-bis(5-6-dichloro-1-methyl-2-benzimidazoylthio) pentane (compound II-33):

0.60 g of 1,5-bis(5,6-dichloro-2-benzimidazoylthio)pentane, 0.37 g of methyl iodide and 0.50 g of potassium carbonate were added to 5 ml of dimethylformamide, and the resultant mixture was stirred at 30°C for 8 hours. After cooling, 10 ml of water was added to the reaction mixture and then the mixture was neutralized with 2 N hydrochloric acid. The crystals thus obtained were collected by filtration and washed with acetonitrile to obtain 0.63 g of the intended compound (yield: 98 %).

Melting point: 141 to 144°C

Elementary analysis for $C_{21}H_{20}N_4S_2Cl_4$:			
Calculated:	C 47.20;	H 3.77;	N 10.49 (%)
Found:	C 47.08;	H 3.69;	N 10.33 (%)

(55) Synthesis of 1,5-bis(5,6-dichloro-1-propyl-2-benzimidazoylthio) pentane (compound II-34):

0.60 g of 1,5-bis(5,6-dichloro-2-benzimidazoylthio)pentane, 0.32 g of propyl bromide and 0.50 g of potassium carbonate were added to 5 ml of dimethylformamide, and the resultant mixture was stirred at 30 °C for 24 hours. After cooling, 10 ml of water was added to the reaction mixture and then the mixture was neutralized with 2 N hydrochloric acid. The oily product thus obtained was extracted with ethyl acetate, washed with water and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (silica gel 30 g, solvent: chloroform). 0.55 g of the intended compound was obtained as an oily substance (yield: 78 %).

(56) Synthesis of 1,8-bis(1-methyl-2-benzimidazoylthio)octane (compound II-35):

0.62 g of 1,8-bis(2-benzimidazoylthio)octane, 0.47 g of methyl iodide and 0.62 g of potassium carbonate were added to 10 ml of dimethylformamide, and the resultant mixture was stirred at 30 °C for 12 hours. After cooling, 10 ml of water was added to the reaction mixture and then the mixture was neutralized with 2 N hydrochloric acid. The crystals thus obtained were collected by filtration and washed with acetonitrile to obtain 0.58 g of the intended compound (yield: 88 %).

Melting point: 117 to 118°C

3) Synthesis of compound (3):

0.42 g (yield: 69 %) of the intended compound (3) was obtained from 0.44 g of the compound (1) and 0.31 g of butyroyl chloride in the same manner as that of Synthesis Example 2).

Melting point: 111 to 113°C

Elementary analysis for $C_{26}H_{30}N_4O_3S_2$:			
Calculated:	C 61.15;	H 5.92;	N 10.97 (%)
Found:	C 60.98;	H 5.89;	N 11.06 (%)

4) Synthesis of compound (4):

0.46 g (yield: 76 %) of the intended compound (4) was obtained from 0.44 g of the compound (1) and 0.34 g of caproyl chloride in the same manner as that of Synthesis Example 2).

Melting point: 69 to 71°C

Elementary analysis for $C_{26}H_{34}N_4O_3S_2$:			
Calculated:	C 62.42;	H 6.36;	N 10.40 (%)
Found:	C 62.23;	H 6.21;	N 10.57 (%)

5) Synthesis of compound (5):

0.55 g (yield: 82 %) of the intended compound (5) was obtained from 0.44 g of the compound (1) and 0.40 g of valeroyl chloride in the same manner as that of Synthesis Example 2).

Melting point: 92 to 93°C

Elementary analysis for $C_{30}H_{38}N_4O_3S_2$:			
Calculated:	C 63.57;	H 6.75;	N 9.89 (%)
Found:	C 63.46;	H 6.57;	N 9.74 (%)

6) Synthesis of compound (6):

1.52 g (yield: 94 %) g of the intended compound (6) was obtained from 0.96 g of the compound (1) and 1.0 g of capryloyl chloride in the same manner as that of Synthesis Example 2).

Melting point: 88 to 89°C

Elementary analysis for $C_{34}H_{46}N_4O_3S_2$:			
Calculated:	C 65.56;	H 7.44;	N 9.00 (%)
Found:	C 65.43;	H 7.27;	N 8.84 (%)

Elementary analysis for $C_{22}H_{26}N_4O_1S_2$:			
Calculated:	C 61.94;	H 6.14;	N 13.14 (%)
Found:	C 61.77;	H 6.02;	N 13.32 (%)

14) Synthesis of compound (14):

0.74 g of 5-chloro-2-mercaptobenzimidazole and 0.84 g of diethylene glycol di-p-tosylate were suspended in 10 ml of acetonitrile, and the resultant mixture was heated under reflux in nitrogen stream for 28 hours. After cooling, water was added to the reaction mixture to dissolve the precipitate, and then the mixture was neutralized with 2 N-NaOH. The crystals thus obtained were collected by filtration and recrystallized from methanol/acetonitrile (1:5) to obtain 0.4 g of the intended compound (14) (yield: 45 %).

Melting point: 90 to 92°C

Elementary analysis for $C_{18}H_{16}C_{12}N_4O_1S_2$:			
Calculated:	C 49.20;	H 3.67;	N 12.75 (%)
Found:	C 49.12;	H 3.58;	N 12.62 (%)

15) Synthesis of compound (15):

0.12 g (yield: 55 %) of the intended compound (15) as a powdery substance was obtained from 0.16 g of the compound (14) and 0.08 g of propionyl chloride in the same manner as that of Synthesis Example 2).

This was a mixture of products having different positions of the acylation, and the products could not be easily separated from each other.

16) Synthesis of compound (16):

0.66 g of 5,6-dichloro-2-mercaptobenzimidazole and 0.65 g of diethylene glycol di-p-tosylate were sluspended in 8 ml of acetonitrile, and the resultant mixture was heated under reflux in nitrogen stream for 28 hours. After cooling, water was added to the reaction mixture to dissolve the precipitate, and then the mixture was neutralized with 2 N-NaOH. The crystals thus obtained were collected by filtration and recrystallized from methanol/acetonitrile (1:5) to obtain 0.64 g of the intended compound (14) (yield: 84 %).

Melting point: 208 to 211°C

Elementary analysis for $C_{18}H_{14}N_4O_1S_2$:			
Calculated:	C 42.53;	H 2.78;	N 11.03 (%)
Found:	C 42.36;	H 2.61;	N 11.24 (%)

17) Synthesis of compound (17):

0.15 g (yield: 67 %) of the intended compound (15) was obtained from 0.20 g of the compound (16) and 0.08 g of propionyl chloride in the same manner as that of Synthesis Example 2).

Melting point: 134 to 136°C

21) Synthesis of compound (21):

0.4 g (yield: 80 %) of the intended compound (21) as an oily substance was obtained from 0.4 g of the compound (18) and 0.4 g of propyl bromide in the same manner as that of Synthesis Example 8).

22) Synthesis of compound (22):

1.5 g of 2-mercaptobenzimidazole and 2.5 g of tetraethylene glycol di-p-tosylate were suspended in 10 ml of acetonitrile. The obtained suspension was heated under reflux in nitrogen stream for 26 hours. After cooling, water was added to the reaction mixture to dissolve the precipitate. After the neutralization with 2 N-NaOH, the oily product thus obtained was extracted with ethyl acetate. The organic layer was washed with water, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 80 g, solvent: 10 % ethyl acetate / chloroform) to obtain 1.8 g (yield: 79 %) of the intended compound (22).

Example 3

The effects of antihyperlipemic agents and antiarteriosclerotic agents each containing a benzimidazole derivative represented by the formula III of the present invention were examined as will be described below.

Pharmacological tests

(1) In vitro tests on inhibition of foaming of macrophage with mouse peritoneal macrophage:

The necks of 15-week old female ICR mice (Japan SLC) were cut off. After blood-letting, Hanks buffer solution (Nissui Seiyaku Co., Ltd.) was injected into the abdominal cavity of each mouse. The abdomen was massaged and then the buffer solution was rapidly recovered, centrifuged at 1000 rotations for 5 minutes to collect the peritoneal macrophages. The peritoneal macrophases thus collected were then suspended in GIT medium (Wako Pure Chemical Industries, Ltd.), and the suspension was spread on a 24-hole microplate. After the cultivation at 37°C in 5 % CO_2 for 2 hours, the medium was replaced with a Dulbecoo Modified Eagle's MEM medium (Nissui Seiyaku Co., Ltd.). After the cultivation at 37 °C in 5 % CO_2 for additional 16 hours, the following substances were added in the following order:

(1) subject: dissolved in DMSO (Wako Pure Chemical Industries, Ltd.)

(2) Liposome:
PC/PS/DCP/CHOL. = 50/50/10/75 (nmols)
PC: phosphatidyl choline (a product of Funakoshi)
PS: phosphatidyl serine (ditto)
DCP: dicetyl phosphate (ditto)
CHOL.: cholesterol (Sigma).

After further cultivation at 37 °C in 5 % CO_2 for 16 hours, the lipid fraction was extracted with chloroform and methanol. The lipid fraction thus extracted was dissolved in isopropyl alcohol, and the formed cholesteryl ester (CE) was determined by an enzymatic coloring method. The cholesteryl ester-forming rate of each compound was calculated in terms of the ratio thereof to the control. The cytotoxicity was examined by microscopic observation of the shape of the cell.

Thus, it was apparent that the test compound (2) has an excellent blood cholesterol decreasing effect.

(3) Acute toxicity test:

The compound (2) was suspended in 0.5 % Tween 80 solution. The suspension was orally administered to a group of six 8-week ddy mice, and the acute toxcity was observed for one month to find that LD_{50} of the compound (2) was 5,000 mg/kg or above. This fact indicates that the compound of the present invention has only a low toxicity.

Example 4

The pharmacological effects of the compounds given in Table 2 were evaluated in the same manner as that of Example 3.

It is appar nt from the results given in Table 2 that 5 μm of each of these compounds was not cytotoxic. In other words, it is apparent that these compounds have only a low toxicity and is capable of remarkably inhibiting the CE formation rate. Namely, they remarkably inhibit the foaming of macrophages without exhibiting a high toxicity to the macrophases.

(ii) Acute toxicity test:

The compound I-7 was suspended in 0.5 % Tween 80 solution. The suspension was orally administered to a group of six 8-week ddy mice, and the acute toxcity was observed for one month to find that LD_{50} of this compound was 5,000 mg/kg or above. This fact indicates that the compound of the present invention has only a low toxicity.

Example 5 Tablets

Preparation of tablets each containing 25 mg of compound (1) or I-7:

(1) Compound (1) or I-7	10 g
(2) Corn starch	40 g
(3) Crystalline cellulose	45 g
(4) Carboxymethylcellulose calcium	4 g
(5) Light anhydrous silicic acid	500 mg
(6) Magnesium stearate	500 mg
Total	100 g

The above-described components (1) to (6) were homogeneously mixed together. The mixture was compression-molded with a tableting machine to obtain tablets each weighing 250 mg. The tablet contained 25 mg of the compound (1) or I-7. The dosage for adults is: 5 to 30 tablets/day to be taken several times a day.

Example 6 Capsules:

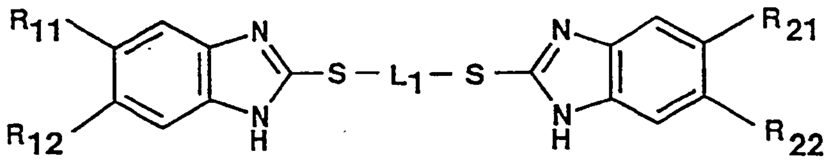
Preparation of capsules each containing 40 mg of compound (1) or I-7:

(1) Compound (1) or I-7	20 g
(2) Corn starch	79.5 g
(3) Anhydrous sinnamic acid	500 mg
Total	100 g

The above-described components (1) to (3) were homogeneously mixed together. A capsule was filled with 200 mg of the mixture. Each capsule contained 40 mg of the compound (1) or I-7. The dosage for adults is: 1 to 20 tablets/day to be taken several times a day.

L_1 and L_2 each represent a connecting group which is an alkylene group or phenylene group-containing alkylene group and when L_1 is a pentamethylene group, both R_1 and R_2 may be hydrogen atoms.

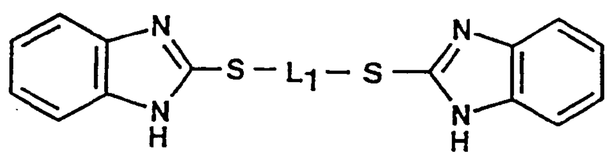
2. The 2-mercaptobenzimidazole derivatives or salts thereof according to Claim 1, wherein the compounds of the formula I are those of the following formula I-I:



I - I

wherein L_1 is as defined above, R_{11}, R_{12}, R_{21} and R_{22} each represent a hydrogen atom, alkyl group having 1 to 18 carbon atoms or halogen atom, with the proviso that both of R_{11} and R_{12}, and R_{21} and R_{22} cannot be hydrogen atoms.

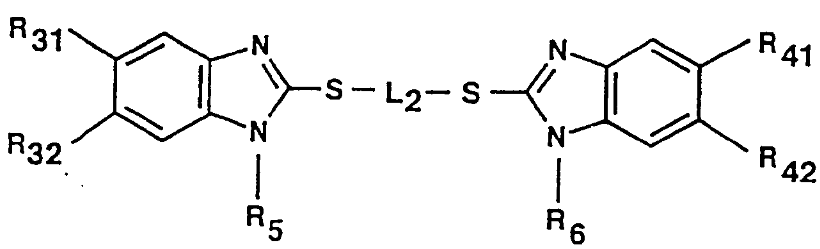
3. The 2-mercaptobenzimidazole derivatives or salts thereof according to Claim 1, wherein the compound of the formula I are those of the following formula I-a:



I - a

wherein L_1 represents a pentamethylene group.

4. The 2-mercaptobenzimidazole derivatives or salts thereof according to Claim 1, wherein the compound of the formula II are those of the following formula II-1:



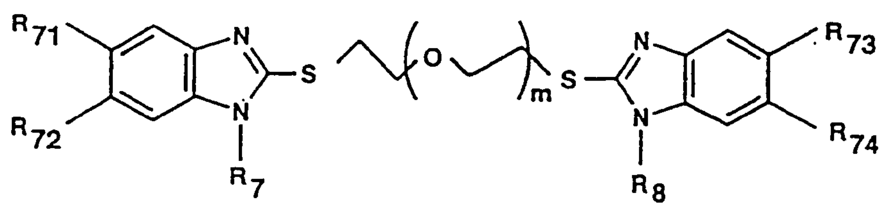
II - I

wherein L_2, R_5 and R_6 are as defined above, R_{31} and R_{32} are the same as R_3, and R_{41} and R_{42} are the same as R_4.

5. The 2-mercaptobenzimidazole derivatives or salts thereof according to Claim 1, wherein the compound of the formula III are those of the folloing formula III-a:

m represents 1, 2 or 3; and
L_2 represents a connecting group which is an alkylene group or phenylene group-containing alkylene group.

11. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 10, wherein the compounds of the formula III are those of the following formula III-a:



III-a

wherein R_7 and R_8 are as defined above. R_{71} and R_{72} are the same as R_9, and R_{73} and R_{74} are the same as R_{10}.

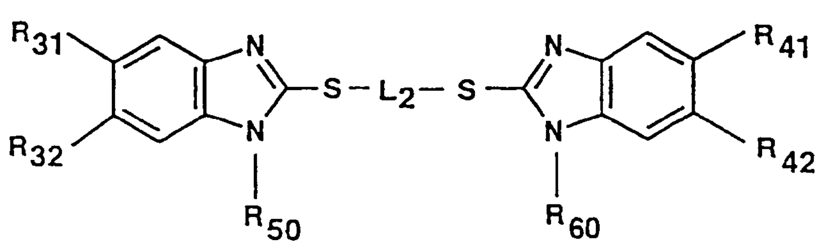
12. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 11, wherein both R_7 and R_8 in the formula III-a represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms or an alkylcarbonyl group having 1 to 8 carbon atoms, R_{71}, R_{72}, R_{73} and R_{74} each represent a hydrogen, and m is 1.

13. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 11, wherein both R_7 and R_8 in the formula III-a represent an alkyl group having 1 to 8 carbon atoms or alkylcarbonyl group having 1 to 8 carbon atoms, one or both of R_{71} and R_{72} represent an alkyl group having 1 to 8 carbon atoms or a halogen atom, and one or both of R_{73} and R_{74} represent an alkyl group having 1 to 8 carbon atoms or a halogen atom, and m is 1.

14. The antiipemic agent or antiarteriosclerotic agent according to Claim 11, wherein both R_7 and R_8 in the formula III-a represent a hydrogen atom, one or both of R_{71} and R_{72} represent a halogen atom or nitro group, one or both of R_{73} and R_{74} represent a halogen atom or nitro group, and m is 1.

15. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 11, wherein both R_7 and R_8 represent a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, R_{71}, R_{72}, R_{73} and R_{74} each represent a hydrogen atom, and m is 2 or 3.

16. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 10, wherein the compounds of the formula IV are those of the following formula IV-a:



IV-a

wherein L_2, R_{50} and R_{60} are as defined above, R_{31} and R_{32} are the same as R_3, and R_{41} and R_{42} are the same as R_4.

17. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 16, wherein all of R_{31}, R_{32}, R_{41}, R_{42}, R_{50} and R_{60} in the formula IV-a are hydrogen, and L_2 represents an alkylene group having 4 to 10 carbon atoms or an alkylene-phenylene-alkylene group (the alkylene having 1 to 2 carbon atoms).

18. The antihyperlipemic agent or antiarteriosclerotic agent according to Claim 16 wherein one of R_{31} and R_{32} and one of R_{41} and R_{42} in the formula IV-a are a hydrogen, and the other is a lower alkyl, halogen, nitro or lower acylamino, and R_{50} and R_{60} each represent a hydrogen, lower alkyl or lower alkanoyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP95/00116

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl[6] C07D235/28, A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl[6] C07D235/28, A61K31/415

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP, B1, 49-46928 (Gevaert-Agfa N.V.), December 12, 1974 (12. 12. 74), Claim, lines 17 to 33, column 2, table of page (3) & US, A, 3704130	1-9 1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
March 6, 1995 (06. 03. 95)	March 28, 1995 (28. 03. 95)
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